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SER. NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/867,819	04/13/92	HARLEY	J OMRF114CIP(C

EXAMINER	
CAPUTA, A	

ART UNIT	PAPER NUMBER
1813	18

18N1/0627

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DATE MAILED: 06/27/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on 3/24/93 (12/21/93) ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. see papers No. 5 and 15
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-20 are pending in the application.
   Of the above, claims 4-6 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 7-20 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☒ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other.

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Part III DETAILED ACTION

1. Applicants' Amendment (Paper No. 17) was entered 3/24/93.

2. The information disclosure statements filed 7/13/92 and 12/17/93 comply with the provisions of MPEP 609. They have been placed in the application file, and the information referred to therein has been considered as to the merits.

3. The prior objection to the use of trademarks is maintained since they should be capitalized (i.e TWEEN) wherever they appear and be accompanied by the generic terminology.

4. The prior objection to the title of the invention is maintained. Applicant state the title has been amended. However, since no amendment can be located in the amendment of Paper No. 7 as asserted said objection is maintained.

5. Applicant's election of peptides 482(481) and 484; Seq I.D. no. 70 in Paper No. 11 of claims 1-11 and 17-20 is acknowledged. Groups 1-III (claims 1-20) are considered a single invention.

6. Newly amended claims 1-2, 6-20 are directed to peptides of 70kD RNP, nRNP A, nRNP C that are independent or distinct from the invention originally claimed for the following reasons: The species (e.g.peptides) are distinct because they are different

proteins and/or different protein coding regions wich differ from one another in amino acid compositon. The peptides appear to be antigenically and immunological distinct as well.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, said species are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

7. The prior provisionally rejection of claims 1-3 and 7-20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11-17, 26, 29, 31, 56, and 64 of copending application Serial No. 07/648,205 is maintained.

Applicant state a terminal disclaimer will be submitted when there are allowable claims. Until a proper terminal disclaimer is provided the rejection is maintained for the reasons stated in the last Office Action.

8. The prior rejection of claims 1-3, and 7-20 under 35 U.S.C. § 112, second paragraph (a),(c), (d) is withdrawn in view of applicants amendment.

9. The prior rejection of claims 1-3, and 7-20 under 35 U.S.C. § 112, second paragraph (b) is maintained.

b. Claims 7-11 and newly amended claims 2-11, are rejected for lack of antecedent basis for claiming peptides (epitopes) in view that the independent claim, claim 1 is claiming a singular peptide (i.e epitope), despite the applicant assertion that the amendment overcomes said rejection.

10. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

11. The prior rejection of claims 1-3, 7-20 under 35 U.S.C. § 101 is maintained.

The specification provides insufficient evidence that the peptide can be used as a vaccine, treatment and diagnosis. The specification provides evidence of the reaction of the elected peptide of normal sera and sera from patients which react with the Ro/SSA protein, however the specification provides insufficient guidance if the reactivity of the peptide with the sera from patients with Ro/SSA is significantly different from normal sera (see Example 2 and Table 2). Further the specification provides no evidence that the epitope is protective in vivo or in vitro. The specification provides no evidence to what extent the peptide (or epitope) is recognized with patients that react with the Ro/SSA protein (1, 2, 10, 50, 95%) and if this epitope is involved in the pathogenesis or protection. The disclosure provides insufficient evidence to the extent the peptide is recognized by sera with patients that have SLE or other diseases and further if the epitope is found in other proteins of other origin which may not be associated with said diseases (i.e., N protein of VSV; see Scofield and Harley, PNAS, 1991). Without evidence that the peptide is protective in vivo or useful for treatment one of ordinary skill in the art would

not use the peptide in the administration of patients as claimed (see claims 7, 8, 9 and 17-20), especially in view that the autoantibodies are implicated in autoimmune disease (see Dryberg et al.) and there is insufficient guidance as to whether the epitope is protective or directly responsible for pathogenesis.

The difficulty in predicting whether a particular in vitro test will be predictive of an asserted in vivo activity has long been recognized. Pharmaceutical therapy is unpredictable in the absence of in vivo clinical data for the reasons described above and for the following reasons:

(1) The protein (peptide) may be inactivated before producing an effect, e.g. such as proteolytic degradation, immunological inactivation or due to an inherently short half life of the protein; (2) The protein may otherwise not reach the target area because for example, (a) the protein may not be able to cross the mucosa, (b) the protein may be adsorbed or absorbed by fluids, cells and tissues where the protein has no effect, and (c) circulation to or in the target area may be insufficient to carry the peptide; (3) A large enough effective local concentration may not be capable of being established; and (4) Other functional properties, known and unknown, may make the protein unsuitable for in vivo use, i.e. may produce adverse side effects prohibitive to the use of such treatment. See M.P.E.P. 608.01(P). See In re Carroll, 601 F.2d 1184, 202 USPQ 571 (CCPA 1979). When the utility of a product is directed to humans, the data must generally be clinical. In order to accept animal data, there must exist an art recognized model for testing purposes. See In re Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962). It is well established that a patent may not be granted on a composition unless a utility is shown other than for experimental purposes only. The burden is on the applicant to demonstrate that the claimed products posses the claimed biological activity. See Brenner v Manson 383 U.S. 519, 148 USPQ 689 (1966).

Applicant assert the patentable utility is to make animal models as drawn to copending application 08/160,604 and to induce tolerance as established in the art. Applicant arguments are not persuasive to overcome the rejection since the assertion of the use of peptides to make animal models is not disclosed in the specification as presented. Further applicant's argument that they can be used for tolerance is not sufficient to overcome the

rejection since as stated previously there is no evidence as to whether the peptides are useful for treatment or therapy which in the Examiner's position apply for use in tolerance as argued by applicants. Applicants evidence of the peptide not reacting with normal sera are noted. However it remains unclear to its use of the peptide since the disclosure provides insufficient evidence to the extent the peptide is recognized by sera with patients that have SLE or other diseases and further if the epitope is found in other proteins of other origin which may not be associated with said diseases (i.e., N protein of VSV; see Scofield and Harley, PNAS, 1991). For reasons described above and in the last Office Action said rejection is maintained.

12. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and/or use the claimed invention, i.e. failing to provide an enabling disclosure.

a. The specification is not enabled for the use of the claimed invention because the utility of the invention has not

been proven for the same reasons outlined in the rejection under 35 U.S.C. § 101.

The specification further fails to teach how to use the claimed peptide for treatment or diagnosis, how to formulate the pharmaceutical composition and guidance to the method of treatment or diagnosis. The specification fails to provide substantive in vivo evidence or a working example that the administration of peptides results in the desired immune response. The specification fails to provide evidence that the peptide is specific for diagnosis and the extent that the peptide is recognized from the sera of patient with autoimmune disease(s). The specification further fails to provide the information required to use the protein such as the amount of protein to administer, the method of administration, the frequency of administration, etc. as a vaccine or for binding and neutralization of autoantibodies. Accordingly it would require undue experimentation for one of ordinary skill in the art to use the protein, and methods to achieve the desired response for treatment or use for diagnosis.

Applicant argues are they can be used for diagnostic uses such as RIA, ELISA, or others. However, since the specification provides 1. no evidence to what extent the peptide (or epitope) is recognized with patients that react with the Ro/SSA protein (1, 2, 10, 50, 95%) and 2. the extent the peptide is recognized by sera with patients that have SLE or other diseases since the epitope is found in other proteins of other origin which may not be associated with said diseases (i.e., N protein of VSV; see Scofield and Harley, PNAS, 1991) it is the Examiner position that it is unclear how to use the claimed peptides for diagnosis.

Applicants argue that it is well established what kinds of doses are required to induce tolerance or the amount to determine the optimal amounts required. Applicant arguments are not persuasive since the specification provides no guidance to what particular quantitative level of antigen is useful for tolerance.

Accordingly, for the reason stated above and set forth in the last Office Action said rejection is maintained.

b. The specification provides evidence of two octapeptides beginning with the amino acid numbered 481-484-489 that are recognized by anti-Ro/SSA (see Table 2). The specification however provides insufficient evidence to which region of the octapeptide recognizes the antibody and peptides of up to 40 amino acids in length as claimed. It would not have been expected that all the peptides (i.e. 4-7 amino acids in length) would have been useful as claimed in view that the peptides would not share the same amino acid composition and therefore the epitope which recognizes the antibody as claimed. In view that the applicant's have provided no guidance beyond octapeptides it would have been undue experimentation to determine which portions of the peptides recognize the epitope as claimed.

Further in view that the additions of amino acids to the peptide alter tertiary structure and the recognition of antibody to the antigen it would have been undue experimentation to determine which additions to the octapeptides would not affect the structure and binding of the peptide to the antibody (i.e. epitope) that encompass the peptides as broadly claimed.

Applicants argue they have listed the exact amino acid sequences which were experimentally shown to react with autoantibodies. Applicant arguments are noted. The specification provides evidence of two octapeptides beginning with the amino acid numbered 481-484-489 that are recognized by anti-Ro/SSA (see Table 2). However the specification however provides insufficient evidence to smaller peptides and peptides of up to 40 amino acids in length as claimed. It would not have been expected that all of the smaller peptides would have been useful since they would not share the same amino acid composition and therefore the epitope which recognizes (i.e. bind) the antibody as claimed. Applicants further appear to argue that since the peptide has a linear epitope the tertiary structure is not

relevant. It is the Examiner's position that the additions of amino acids to the peptide alter structure and the recognition (e.g. binding) of antibody to the antigen due to ionic or covalent binding between amino acids of a peptide. Accordingly, it would have been undue experimentation to determine which additions to the octapeptides would not affect the structure and binding of the peptide to the antibody (i.e. epitope) that encompass the peptides as broadly claimed.

c. With regards to claim 16 the specification provides evidence that sera of patients with a reaction to the 60 kDa protein react with the elected species at greater than a fixed value and less than this value with normal sera. The specification however provides no guidance of the reaction of the elected peptides to autoantibodies and the prognosis of the patient. In view that the specification provides no guidance to the specificity, variability, and how reactivity of the elected peptides and antibody is related the severity of the disease(s) it would be an undue burden to ascertain the use of the method to predict the prognosis of the patient as claimed.

Applicants argue that a higher titer of antibodies correlate with a higher severity of disease. Applicants arguments are not persuasive since applicants have provide no evidence to this correlation. There is no evidence that a particular level of antibody is associated with particular symptom and that each patient would present the same clinical signs with an equivalent concentration of antibody. Accordingly, it would it would be an undue burden to ascertain the use of the method to predict the prognosis of the patient as claimed. For the reason stated above and in the last Office Action said rejection is maintained.

13. Claims 1-3, and 7-20 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

14. The prior rejection of claims 1-3, 8, 10-17, 19, and 20 under 35 U.S.C. § 103 as being unpatentable over Deutscher et al., in view of Harley et al. Dryberg et al., Geysen et al. and Voller et al. is withdrawn in view of applicants arguments.

15. The prior rejection of claims 1-3, and 7-20 are rejected under 35 U.S.C. § 103 as being unpatentable over Deutscher et al., in view of Harley (U.S. Patent No. 4,784,942), Hopp (U.S. Patent No. 4,554,101), and Voller et al. is withdrawn in view of applicants arguments.

Thus the claimed invention as a whole is clearly prima facie obvious, especially in the absence of evidence to the contrary.

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Barakat et al. teaches of two C-terminal fragments (495-518, and 524-538) had no antigenic activity (see Discussion, 1st paragraph).

Ben-Chetrit et al. teaches of the cDNA sequence of the 60 kDA SSA/Ro protein.

Frank et al. (WO 91/17171) teaches that portions of the Ro/SSA antigen are useful for diagnosis and for treatment.

17. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

18. Any inquiry concerning this communication should be directed to Dr. Anthony C. Caputa, whose telephone number is 703-308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is 703-308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-308-4227.

Anthony C. Caputa, Ph.D.

June 27, 1994

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180